

**SOME BREAKTHROUGHS TURN OUT TO BE REALLY SMALL**

**2011 – THE REVOLUTION OF NANOTECHNOLOGY**

**By**

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## **Abstract**

Nanotechnology is recognised by scientists all over the world as the technology of 21<sup>st</sup> century. Entering a new era of technology, we now are experiencing a new face of science and a new way to diagnose diseases. This paper presents the development of nanotechnology and its recent uses in the treatments of various medical problems, in particular cancer, compared to the conventional treatments.

## **INTRODUCTION**

Nano- refers to the size of  $10^{-9}$  of a meter. Nanotechnology is the engineering functional systems at the molecular scale.

The starting point of nanotechnology:

'Nanotechnology' originally referred to the projected ability to construct items from 'the bottom up', making high performance products from our current tools and techniques.<sup>1</sup>

In 1959, there was a quote that opened the concept of 'Nanotechnology'. "There's plenty of room at the bottom"<sup>2</sup> – a quote suggesting that instead of disassembling materials, we can assemble really small things, in other words, on atomic scale<sup>3</sup>. Specifically, his idea was that computer devices could be minimised, in which "wires should be 10 or 100 atoms in diameter".

Following this idea, in 1986, Eric Drexley published a book called 'Engines of Creation'. It was developed from his vision that tiny machines, which are built atom by atom, will be used for various purposes. It can diagnose and cure diseases once entering the bloodstream or remove pollutants in the air. His vision has urged chemists, computer scientist and engineers to focus their research on nanoscale.

Scanning Tunelling Microscope (STM) was invented by Gerd Bining and Heinrich Rohrer in 1981. It was a powerful microscopic technique that can magnify particles which are 1/25 the size of a molecule. It forms image of individual atoms on a metal or semiconductor surface by scanning the tip of a needle over a surface at a height of only a few atomic diameters. It enables us to identify the roughness of the surface and the size of the molecules on the surface.<sup>4</sup>

Fullerene (C<sub>60</sub>) is other form of pure carbon apart from diamond and graphite. It consists of 60, 70 or more carbon atom. Fullerenes comprise of a spherical, ellipsoid, or cylindrical arrangement of dozens of carbon atoms.<sup>5</sup> It was accidentally discovered in 1985 by Professors Robert F. Curl, Jr., Richard E. Smalley of Rice University, Houston, USA and Sir Harold W. Kroto at Sussex University, Brighton, UK during the experiments on laser vaporisation of carbon.

Fullerenes are antioxidants and react readily with free radicals. Therefore, it can be used to prevent oxidative cell damage. Particularly, research on whether fullerene can control neurological damage of diseases like Alzheimer's disease and Lou Gehrig's disease are carried out by many pharmaceutical companies. In addition, fullerene is also a MRI agent in imaging.<sup>6</sup>

# **DISCUSSION**

## **A) APPLICATIONS**

The properties of materials built from nanotechnology can be observed and examined on microscale as well as macroscale and is used to develop other materials, tools with new approaches and functions. The small sizes of nanoparticles make them suitable for various medical uses.

### **1 - *Anti ultravirus***

Vancomycin has known to be one of the few antibiotics that can work against the rapidly resistant diseases, such as MRSA. Nevertheless, there is resistant strain against Vancomycin, known as Vancomycin-resistant Enterococci (VRE), which is a major problem on human health. According to the Health Protection Agency, during 2007 there were 7000 of MRSA and more than a thousand cases of VRE in England. This increase in the number of fatal infections urges the development and the advance of technologies to fully understand how antibiotic works.

Dr Mckendry, Joseph Ndieyira, Moyu Watari at the London Centre for Nanotechnology (LCN) at UCL used cantilever arrays, which is less than a human hair, coated with mucopeptides to examine the process when vancomycin antibiotic is contact with the surface of the bacteria. According to their observations, they discovered that when the antibiotic attaches itself onto the bacteria, it creates a pressure against the surface of the bacteria, disrupting the cell walls. By that way, it can breakdown the bacteria.

However, there are some mutant strains, referred to as 'superbugs' which delete the hydrogen bonds in the structures of their cell walls, making it difficult for the antibiotic to attach on the bacteria. Therefore, the breakdown of the bugs' cell walls is not viable and the antibiotic is as a result become ineffective.

The cantilever sensors reveals the possibility that if we can investigate and combine the effect of both local antibiotic mucopeptide binding and the spatial mechanical connectivity of these bindings, we can develop new antibiotics that works against the most resistant strains.<sup>7</sup>

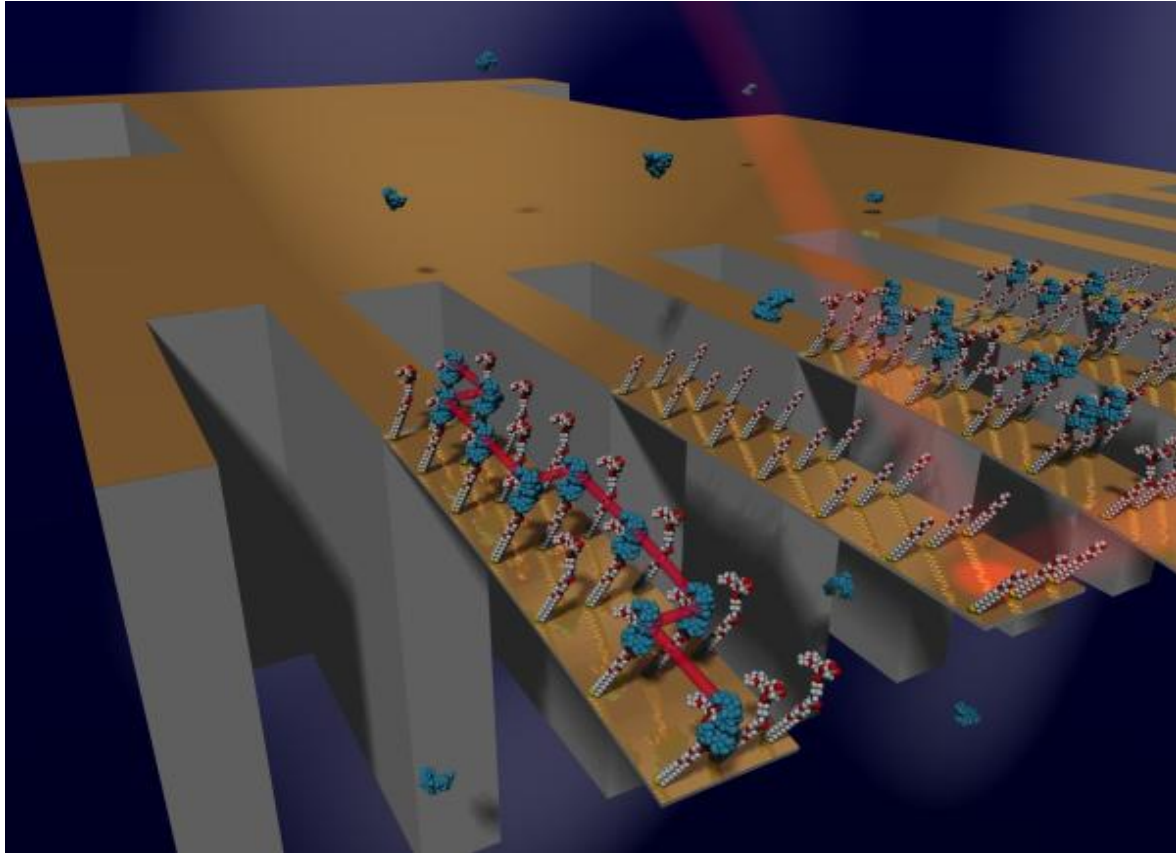


Figure 1: Nanomechanical detection of antibiotic peptide interactions on multiple cantilever arrays.

The blue and white structures: chemical binding interaction between vancomycine and bacterial mucopeptide analogue

Red line: mechanical connectivity of the chemically reacted regions on the cantilever.

## **2 - Cancer treatment**

The conventional ways of treating cancer such as surgery, radiotherapy, chemotherapy have been popular for a long time but suffer from limitations: its non-specificity, high toxicity to normal cells, easily eliminated by circulatory system and taken by lymphatic system. This can result in the incomplete removal of tumour cells or potentially fatal side effects, such as hair loss, nausea, hearing loss when receiving intravenous infusing of chemotherapy.<sup>8</sup>

What we need is a technique that can target the diseased cells to make the use of drug effective and reduce the toxicity. There are differences between normal cells and cancer

cells that enables targeting, including tumour markers, extracellular matrix, soluble factors, proteases and its unique architectural and transport properties. The nanodevices improves the sensitivity in detecting cancerous tissues, screening tests and the specificity and efficiency in targeting cancer cells.<sup>9</sup>

There are several techniques involving nanotechnology in cancer treatment.

### 1) Passive targeting

It relies on the pharmacokinetic of nanoparticles, such as the effect of Enhanced Permeability and Retention (EPR) to select the tumour cells. It takes the advantage of the permeability of the tumours. Due to their leaky blood vessels and the poor drainage to the lymphatic systems, nanoparticles which are smaller than 100nm will remain in cancer cells but not entering healthy cells. Attachment of polymers such as poly(ethylene glycol) (PEG) and poly(ethylene oxide) (PEO) prevent the nanoparticles being taken by mononuclear phagocytes in the liver, lymph nodes thus increase accumulation in the tumour.<sup>10</sup>

### 2) Active targeting

It involves attaching ligands to the nanoparticles. These ligands can bind to complementary molecules, or receptors found on the surface of tumour cells. They are used to target the tumour cells, allowing more drugs molecules to enter the cancer cells and reducing the influence on surrounding normal cells.<sup>9</sup> There are many types of ligands used for treating cancer. Cadherins, which are glycoproteins, are used to facilitate calcium ion dependent cell – cell adhesive interaction.<sup>11</sup> Human holo-Tf (transferrine) is also a targeting ligand conjugated onto gold-nanoparticles.<sup>12</sup> Others are liposomes and integrins.

### 3) Remote Actuation

Cancer can be treated remotely by inorganic nanomaterials. These materials absorb electromagnetic or ultrasonic energy that can trigger thermal ablation or drug delivery to the cancer cells.

In particular case, for example, gold nanoshells are used in both targeting and thermal ablation to treat cancer. Gold nanoshell contains the core (interior part) made of silica and the shell, which is a thin layer of gold. The nanoshells are coated with PEG and anti-EGFR (anti-epidermal growth factor receptors). These nanoshells are 'tuned' to absorb the wavelengths of light within a useful range, which are outside the visible spectrum and near-infrared light. The advantages of leaky blood vessels (as in passive targeting) and the expression of EGFR on cancer cells (as in active targeting) are applied here to localise the tumour.

Gold is an inert metal and it displays very strong plasmon resonance effects\*. Once the nanoparticles have targeted and attached to the cancer cells, near-infrared light passes through the body and is received by these gold nanoshells. The nanoparticles use their surface plasmon resonance effect to convert light into heat and kill the cancer cells. Dead cancer cells are consumed by phagocytosis, and healthy cells are remained.<sup>13</sup>

**\*Surface plasmon resonance effect:** the interaction between metallic nanoparticles and electromagnetic waves in which the electrons along the surface of metallic nanoparticles are excited by light and begin to oscillate

## Other cancer treatments

### I) Magnetic Iron-oxide

Magnetic nanoparticles is used to treat ovarian cancer. The problem with ovarian cancer is that the malignant cells can spread from tumour to the fluid in the abdominal cavity. These free-floating cells then move to other organs, causing further metastasis. The treatment consists of the magnetic nanoparticles, made of cobalt-iron core, combined with a short synthetic peptide, which binds with Ephrin A2. This is a protein that is expressed at high levels on the surface of free-floating ovarian cells. Studies showed that cancer cells from the abdominal fluid of mice carrying human ovarian cells are trapped by these nanoparticles. Further studies on the fluid from the cancer patients showed that all Ephrin A2-positive cells (free-floating ovarian cells) could be trapped and removed. This can reduce the chance of metastasis that may occur. Making use of magnetic nanoparticles to remove cancer cells from abdominal cavity, combining with chemotherapy or radiotherapy, is an effective treatment for ovarian cancer.<sup>14</sup>

### II) Folate-targeted Dendrimers

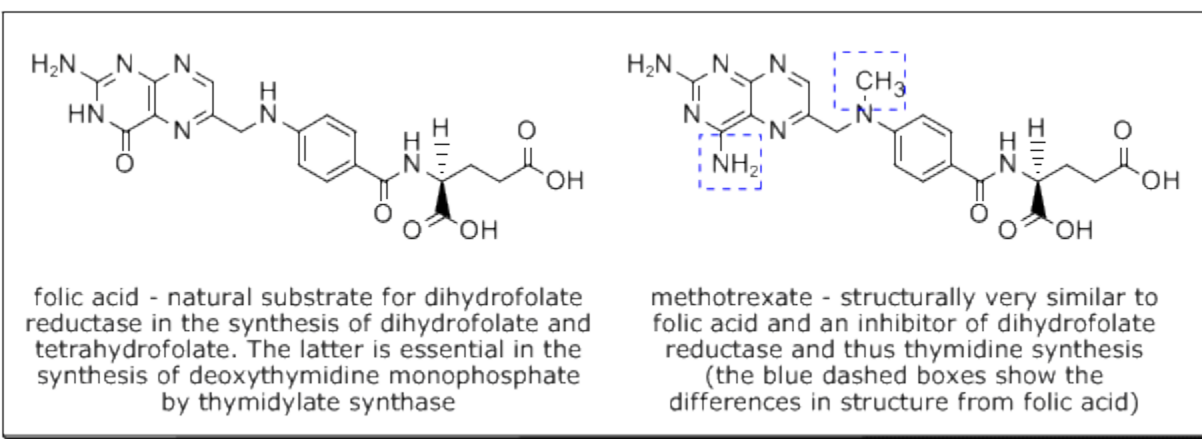


Figure 2<sup>15</sup>

Dendrimer molecules, which are highly branched polymeric molecules, have 'multi-arms'. This highly branched structure allow the attachments of other drugs. Polyaminoamine (PAMAM), highly biocompatible, non-toxic and biodegradable<sup>16</sup>, is a popular dendrimer.

In normal human epithelial tissues, type- $\alpha$  folate receptors expressed in small amount. Significant amount of the same receptor is found on malignant cells in lung, colon and ovarian cancer. This creates the target for drug delivery.

Figure 2 shows the structures of folic acid and methotrexate. Though having similar structure, they have different functions. Folic acid is beneficial for cancer cells as it stimulates the replication of DNA. It is therefore required in vast amount to enable the rapid and uncontrolled division of cells. Methotrexate, in contrast, disrupts the synthesis of DNA and RNA and therefore inhibits the division of cells.

Both folic acid and methotrexate are conjugated to the dendrimer. As folic acid and its receptor are complementary, folic acid enables the better target for cancer cells. When cancer cells accept the dendrimers, methotrexate is released into the cells and it acts as cancer-killing agent.

Furthermore, Gadolinium, because of its paramagnetic property, can be conjugated to the dendrimer for Magnetic Resonance Imaging (MRI). It helps to create the image of blood vessels, tumour or inflammation.

This technique has combined properties of tumour-targeting molecule (folic acid), current chemotherapy drug (methotrexate) and imaging agent.<sup>9</sup> Therefore, it can be used in cancer treatment with targeting, imaging and drug delivery capabilities.

An experiment is carried out by researchers, led by Francis Szoka, Ph.D., of the University of California, San Francisco, and Jean Fréchet, Ph.D., of the University of California, Berkeley to see the effect of polymeric drug delivery has on colon cancer in mice.

On one half of the dendrimer, they attached poly(ethylene glycol) (PEG) in order to make the dendrimer water-soluble. On the other half, doxorubicin, an anticancer drug was conjugated to the dendrimer by a chemical linkage. This linkage breaks when exposed to acidic condition. The reason for that is while the pH of the bloodstream is neutral, the pH of tumour cells are acidic. When the bond breaks, drug is released into the cells

The experiment lasted for 60 days with the use of either dendrimer-doxorubicin formulation or free doxorubicin on mice. After 24 days, none of the mice treated with

doxorubicin only survived. Other mice which were treated with dendrimer survived until the end of the period, showing the tumour completely removed and fewer side effects.<sup>17</sup>

### **3 - Other uses - Carbon nanotubes**

There are 2 types of nanotubes: single-walled nanotubes (SWNTs) – a single layer of graphite wrapped into a seamless cylinder and multi-walled nanotubes (MWNTs) – many layers of graphite are rolled into tubes.

Nanotubes exhibit various unique properties. Because its electronic structure is nearly one dimensional, electric transport in metallic SWNTs and MWNTs occurs ballistically (without scattering). Therefore, they are superconductors. At room temperature, theoretical work predicts the thermal conductivity of individual nanotubes of 6600W/mK. Measurements show that the thermal conductivity of a bulk samples of SWNTs was 200W/mK and over 3000W/mK for a single MWNT<sup>18</sup>. Moreover, small diameter SWNTs also have high Young's modulus and high tensile strength, which make them stiff and extremely strong. As they can be extended elastically by about 5.8% before breaking, SWNT can withstand the pressure of 37GPa.<sup>19</sup>

Carbon nanotube transistors give us the idea that nanotubes can be used as wires, which can be rendered into conducting, semiconducting or insulating state, for nanocomputer design.<sup>20</sup>

The thermal properties of carbon nanotubes make it useful for a number of thermal applications, such as heat silicon sinking processors or to increase the thermal conductivity of electric motors.<sup>17</sup>

The high Young's modulus and light weight make carbon nanotubes ideal reinforcing agents in many composite materials used in aircraft and sports industries.

Due to the large surface area compared to relative small mass, SWNTs may be potential materials for hydrogen storage. In theory, they can store hydrogen up to 7.7 wt%. It is promising that nanotechnology may contribute to the future of renewable energy.<sup>21</sup>

## **B) POSSIBLE DANGERS**

Long-term effects of using nano-products are still unknown.

- In 2004, biologist Eva Oberdoster of the Duke University Marine Laboratory in Beaufort, North Carolina and Southern Methodist University in Dallas revealed that Fullerenes, the most well-known nanomaterials had physiologic impacts on aquatic organisms. After the exposure of 48 hours, the fish showed damages to their brain, possibly due to the oxidative reactions. Moreover, the fish also exhibited the changed gene expression and inflamed chemical marker, which is the cause of increasing number of diseases.

A research was carried out in a controlled laboratory study. The researcher exposed nine juvenile largemouth bass, confined to 10-Liter aquaria to water-soluble buckyballs at a dose of 0.5 parts per million. After 48 hours, the fish showed signs of brain damage by lipid peroxidation. The damage, compared to those unexposed animals, was 17 times higher.

By further observation, Oberdorster found that the water in the fullerene tank was clearer than in control tanks. This might due to the influence of fullerene on a kind of bacteria which is beneficial to the fish, and that affected the food chain.<sup>22 23 24</sup>

- In 2004, Dr Vyvyan Howard presented findings in which nanoparticles can penetrate maternal placenta to the fetus. A recent study published by Environment Health Perspective shows that plastic nanoparticles can move from mother to baby through placenta. Toward the end of pregnancy, the membrane between mom and fetus becomes thinner. Therefore, small-sized nanoparticles can cross the barrier and may be contact with the growing brain, or other organs of the fetus.

In their research, nanoparticles made from polysterene were injected into mothers' placenta right after the babies were born. These nanoparticles were of different sizes: 50, 80, 240 and 500 nm and they were fluorescent so their travel could be indentified. Within 15 minutes after the infection, the small nanoparticles, sizes 50, 80 and 240 nm were found on fetal side, whereas the 500nm-sized remained on maternal side.<sup>25 26</sup>

So far, lab studies have shown that airborne materials affect brain, DNA and lung function. Also, animal studies showed reproductive changes, embryo death and nerve damage. Research on human is still carried out if the fetus is at risk.

Nanoparticles have had impacts on environmental and human aspects. As the potential toxicity is still unknown, further studies and research should be carried out.

### **C) ETHICAL ISSUES**

1. Futurist Ray Kurzweil believes that in 30 to 40 years' time, human will reach immortality, thanks to Nanotechnology. By 2050, we will have nanorobots which travel in our bodies, repairing damaged cells and organs. Nanotechnology will soon have products that resemble our internal organs. Those products will not age and die.<sup>27</sup>

However, as natural occurrence, the birth rate and death rate are supposed to be balanced. In fact, the global population is exponentially increasing. If Kurzweil's prediction is true, what would happen to the human race in which everyone could live forever? More demands on energy, foods, space or even social problems can occur if there are too many people on earth.

2. Nanotechnology will advance researches on stem cells. The use of stem cells is still controversial. Furthermore, rather than getting cells from reproduction, it is easier to construct cells according to our desires. Many religious groups oppose it.
3. Grey goo – the scenario in which nanorobots made by molecular nanotechnology will self-replicate and consume all matter on Earth<sup>28</sup>. Bill Joy said in Wrote: “In the wrong hands, nanotech could be more destructive than a nuclear bomb”<sup>29</sup>. “So-called grey goo could only be the product of a deliberate and difficult engineering process, not an accident,” said Phoenix. “Far more serious is the possibility that a large-scale and convenient manufacturing capacity could be used to make incredibly powerful non-replicating weapons in unprecedented quantity. This could lead to an unstable arms race and a devastating war. Policy investigation into the effects of advanced nanotechnology should consider this as a primary concern, and runaway replication as a more distant issue.”<sup>30</sup>
4. Without awareness, nanotechnology can be turned into military weapons for political purposes.

Nanoengineered weapons will be the greatest threat to human. Nanotechnology holds trillions of lives, in other words, every living organisms on Earth. Dramatically, nanotechnology may lead to the destruction of the entire world.<sup>31</sup>

Overall, we should take into consideration the limit of the uses of nanotechnology, to what extent nanotechnology should be in order not to misuse the sense of science, but to develop human lives in a morally acceptable way.

#### **D) FUTURE OF NANOTECHNOLOGY**

The preliminary achievements seem to open more ideas that nanotechnology can bring to us. In my opinion, we can develop a type of nanoparticles which can penetrate cell membrane in order to kill the virus inside the cell. In that way, the cures for HIV or other viral diseases are viable. Other uses of nanotechnology that can be considered is that, as carbon nanoparticles are very strong and hard, it can be used to strengthen bones in bone repair treatments. Moreover, we can potentially create a nanomachine, which is selectively permeable and acts like a filter, in order to treat kidney failures.

#### **E) ATTENTION OF MANY COUNTRIES' GOVERNMENT**

Though nanotechnology is a newly-introduced science, it has the potential of completely changing our lifestyles. Therefore, nations throughout the world have paid extreme attention and set goals to research, develop and apply nanotechnology so as to encourage and aid the developments of economic situations, along with other sciences and technologies, such as computer technology, biotechnology.

Each nation involves in nanotechnology with different ways and purposes. USA is known to be a leading country in information technology and biotechnology. Therefore, it is not surprising that the NNI (National Nanotechnology Initiative) budget provided increased support for research on fundamental nanoscale phenomena and processed, from \$481 million in 2007 to \$551 million in 2009.<sup>32</sup>

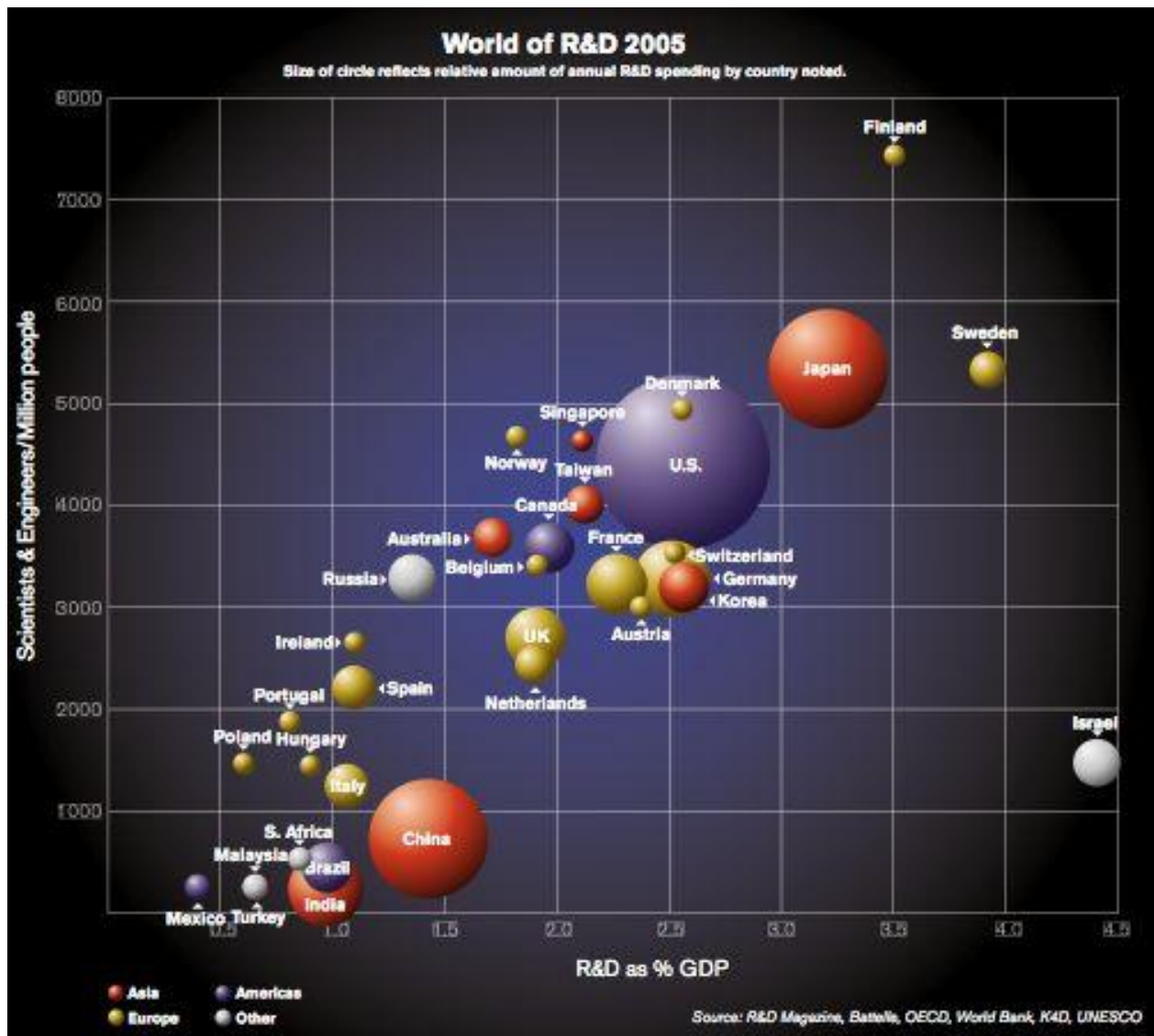


Figure 3

The scattergram (figure 3) shows of nanotechnology funding and scientists/engineers per capita in various countries. It is clear that U.S., Japan and China are the leading countries.<sup>25</sup>

Japan, though focusing on projects to meet social's demands, its government has planned to develop on nanotechnology, with the highest funding in 2003 of 1.6 billion dollar.

Nanotechnology also attracts other Asian countries, such as India, Korea and Taiwan.

Another nation which should be considered in the development of nanotechnology is Israel. Although it is in the Middle East, suffering both political and military pressure, its goal is strongly connected to nanotechnology. Israel uses nanotechnology for urgent issues, such as water and energy supply.<sup>33</sup>

Moreover, Africa is also on its way to the advance of nanotechnology. At present, nanotechnology is built by individuals around various branches and 53 countries in Africa have been using nanoscience and nanotechnology. Focus Nanotechnology Africa Inc. (FONAI) consists of some government sponsored initiatives. Its objective is to provide the proposed budget of \$10 billion for the next 10 years to nanoscience and nanotechnology.<sup>34</sup>

## **CONCLUSION**

From the fact that inventions and achievements are brought to lives at rapid speed, we expect that the world will significantly change shortly. There is hope that nanotechnology will help us to solve the problems, in every aspect, especially medical, that we are struggling to find the answers. A number of diseases will promisingly be cured, e.g cancer, MRSA, HIV.

Nanotechnology will undoubtedly make poverty history. It makes the products cheaper, and make them more accesible to the poor. In short, it brings our world together and betters thousands of lives.

There is still controversy about the uses of nanotechnology. Therefore, cautions should be taken while developing nanotechnology. The limit of using nanotechnology should be applied in order not to raise too much ethical issues. Goverments play the key role in determining the level of developing nanotechnology. Moreover, it is critical as well as unethical to use nanotechnology for making weapons or creating artificial lives.

In addition, more research should be done in order to investigate the long-term effects of nanoparticles. Most of the research are on experimental stage so the insight into nanotechnology is essential.

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